

Workshop on Policy Issues in Development of Personalized Medicine in Oncology

-Technological Hurdles-

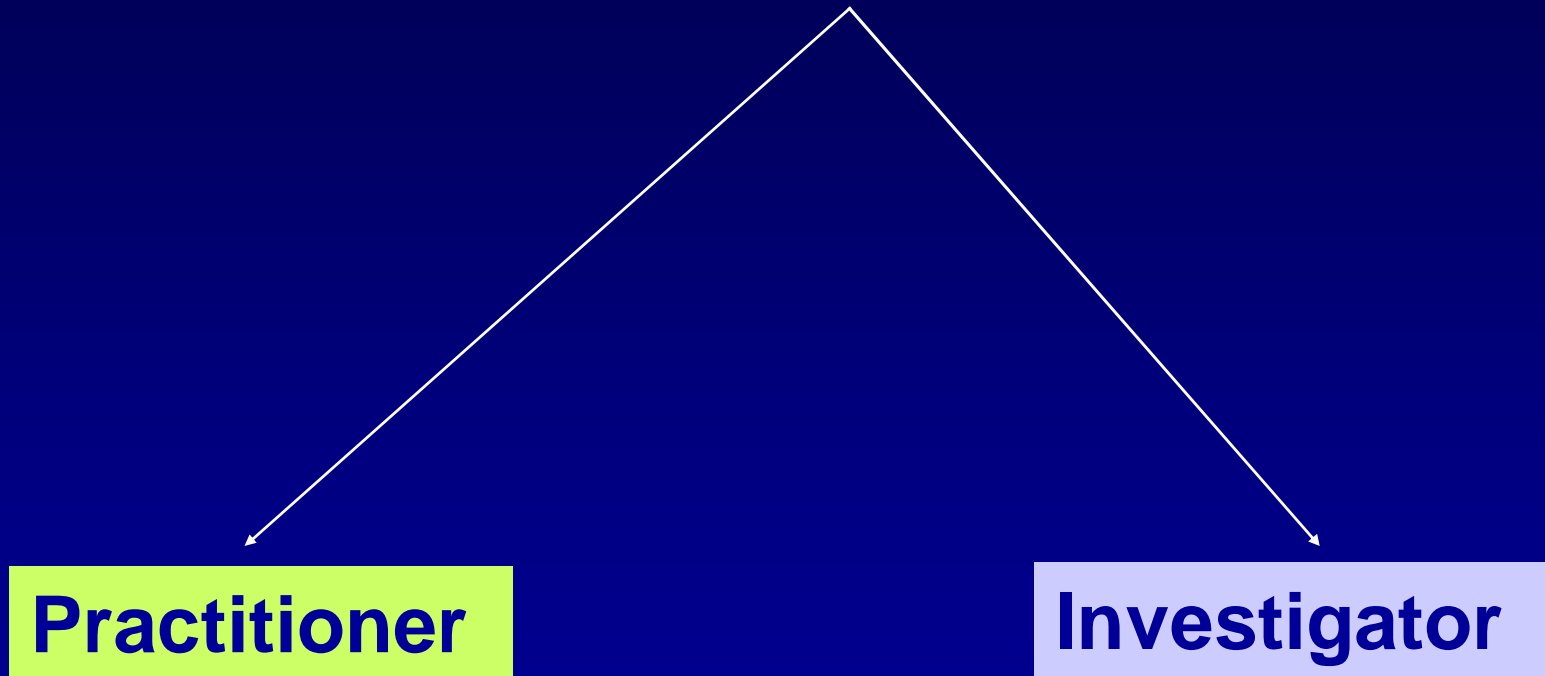
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Clinician Perspective



What Do Doctors Want?

- How will this test help me manage my patient? i.e., Intended use
- Refine prognosis?
- Select treatment?
- Monitor therapy?
- Detect recurrence?

When and How Often?

- At diagnosis? Usually once
- Prior to initiating treatment? Usually once
- During treatment? Repetitively
- During treatment-free intervals? Repetitively

Specimen Acquisition and Handling

- What kind of specimen?
- Obtained in the office or the hospital?
- Is another practitioner involved?
- Does the specimen require special handling?
- Who sends the specimen to the lab, i.e., doctor's staff or hospital staff?

Turnaround Time and Reliability

- How long until I get the test results?
- How is positive/negative defined?
- How reliable are the results?
 - ∅ False positive/negative rates
 - ∅ Inter/intra test variability?
 - ∅ Is there a normal range?
 - ∅ What if the test is wrong???

What Does This Have To Do With Policy?

- What is the claim/approved use?
- How is the test regulated?
- What level of evidence is required for marketing approval?
- What labs can perform it?
- Who pays for it? Once or each time?

Clinician-Investigator Perspective

Key Issues in Clinical Biomarker Development

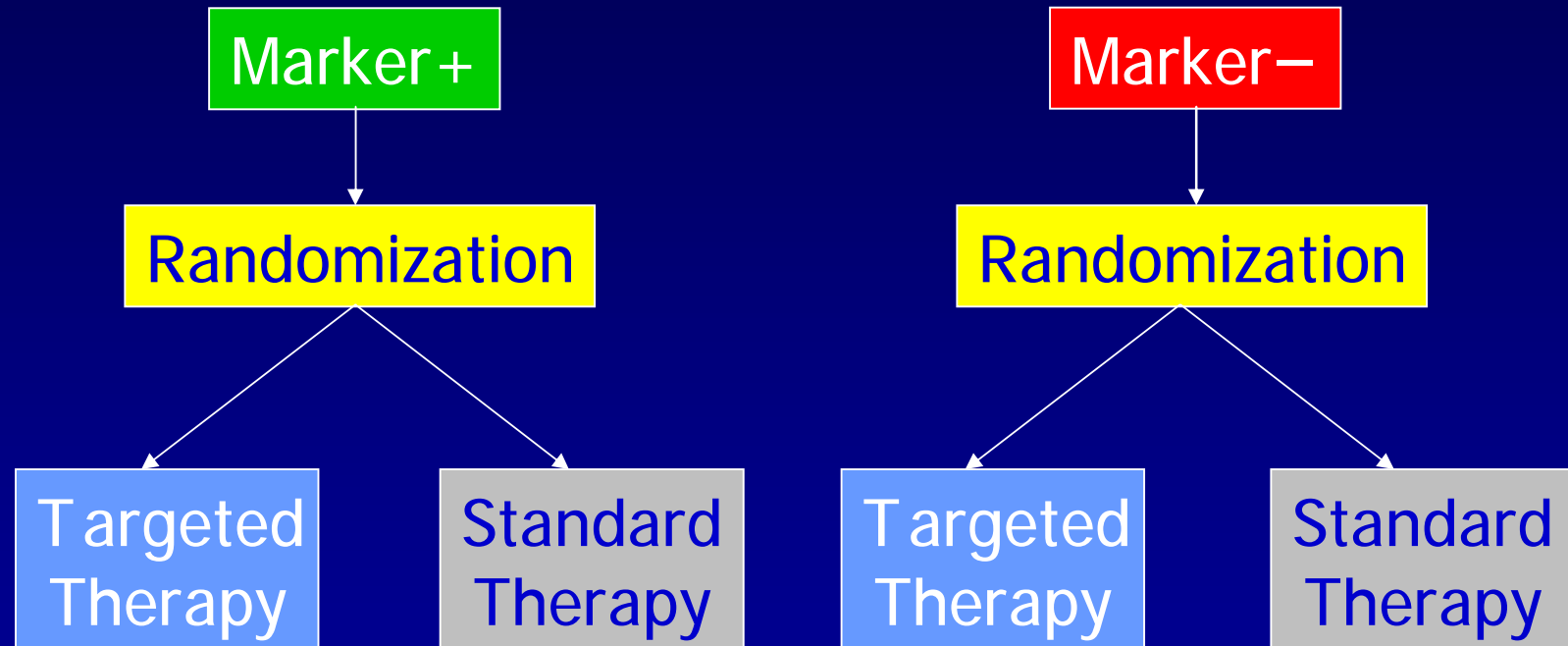
- Define intended clinical use
- State a hypothesis
- Prospectively study the population and/or specimens for the intended use
- Use an analytically validated biomarker test
- Hypothesis and sample size should be adequate to demonstrate improved clinical outcomes when the biomarker test is applied

Types of Biomarker Studies Done by Cooperative Groups

- Exploratory (correlative) studies using clinically annotated biospecimens and research assays
- “Retrospective-prospective” studies using clinically annotated specimens, known clinical outcomes and research or analytically validated assays
- Prospective biomarker-drug co-development studies
- Prospective biomarker development studies
- Prospective biomarker validation studies

Prospective Marker Validation Studies

The most informative design



N0723: Predictive Marker Study Design

NCCTG (Study Chair: Alex Adjei) + CALGB, ECOG, SWOG, NCIC
Others: C-Path & industry partners, Pharma

Initial Registration

2nd line
NSCLC
with
specimen

FISH
Testing

Strata

EGFR FISH +
(~ 30%)

EGFR FISH -
(~ 70%)

Randomize

Erlotinib

Pemetrexed

Erlotinib

Pemetrexed

957 patients

Outcome

1° PFS
2° OS, ORR

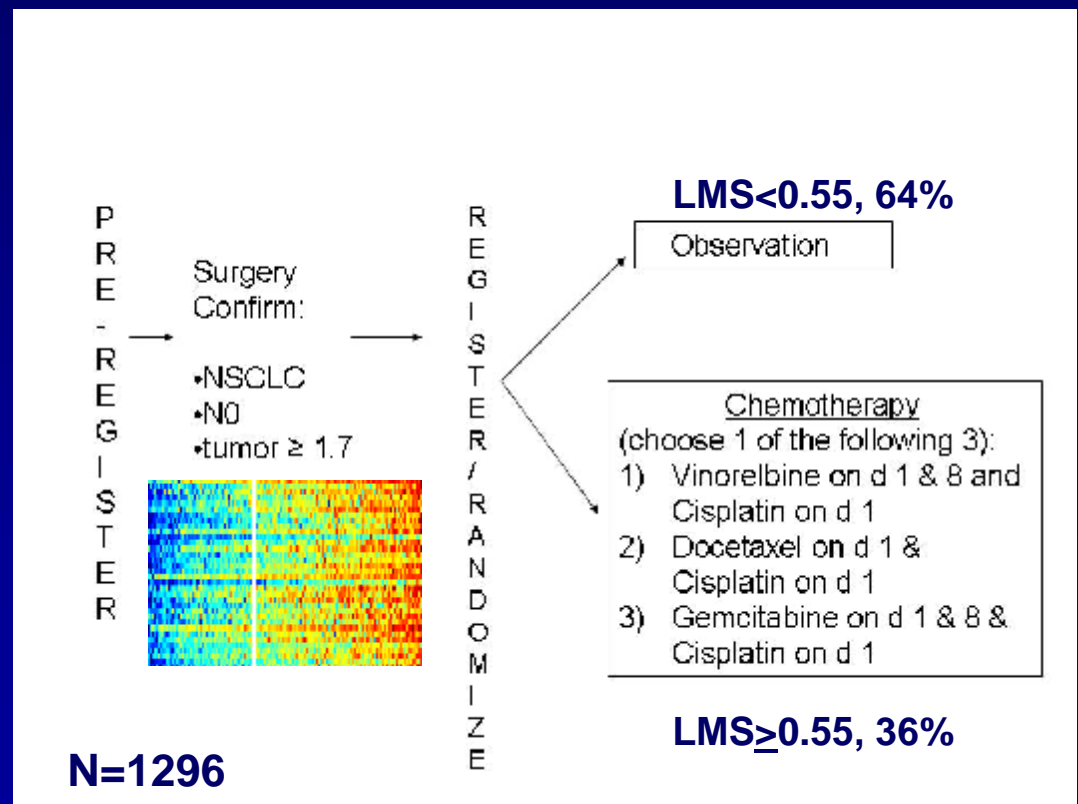
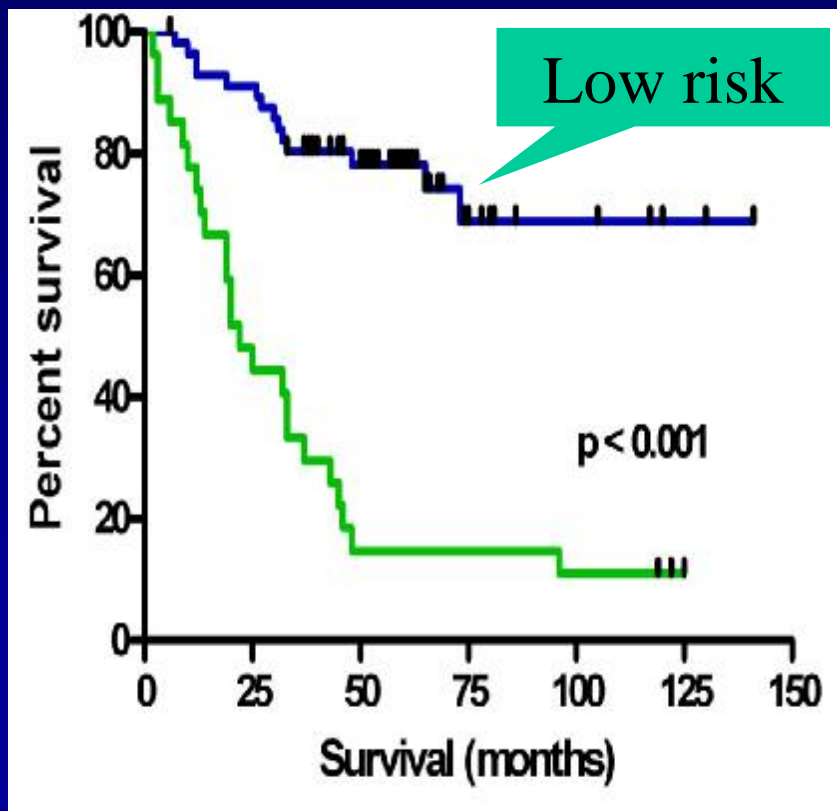
1-2 years
minimum
additional
follow-up

4 years accrual, 1196 patients

- PFS endpoint
 - Less influenced by treatment crossover
 - Will require synchronized treatment schedules, independent blinded imaging review
- Power
 - 90% to detect 50% PFS improvement favoring erlotinib in FISH+, 2.5---3.75m
 - 90% to detect 30% PFS improvement favoring pemetrexed in FISH-, 1.92--2.5m
 - > 90% to detect interaction

CALGB 30506

A randomized phase III trial to evaluate the potential utility of a genomic prognostic model to identify stage I non-small cell lung cancer patients as candidates for adjuvant chemotherapy



Assumptions

5 Year Overall Survival

	High Risk	Low Risk
Chemotherapy	60%	73%
Observation	45%	68%

Power > 95% to detect hypothesized effect of Chemo overall and in high risk group and hypothesized difference in OS between high and low risk groups on OBS arm

TailoRx

NODE NEGATIVE BREAST CANCER STUDY

ER/PR + tumors



ONCOTYPE DX ASSAY

Score < 11
29% of pts

Score 11-25
44% of pts

Score >25
27% of pts

R

Endocrine
Therapy

Endocrine
+
Chemotherapy

Chemotherapy +
Endocrine Therapy

Accrual goal= 4800 randomized patients, 11000 screened

Non inferiority = decrease in 5 year DFS from 90 to 87% or less

Biomarker-Drug Co- Development

Clinical Trial Study Designs

- If we are confident that the therapy will not work in Marker-negative patients

AND

- We have a validated assay that can reliably assess the status of the Marker

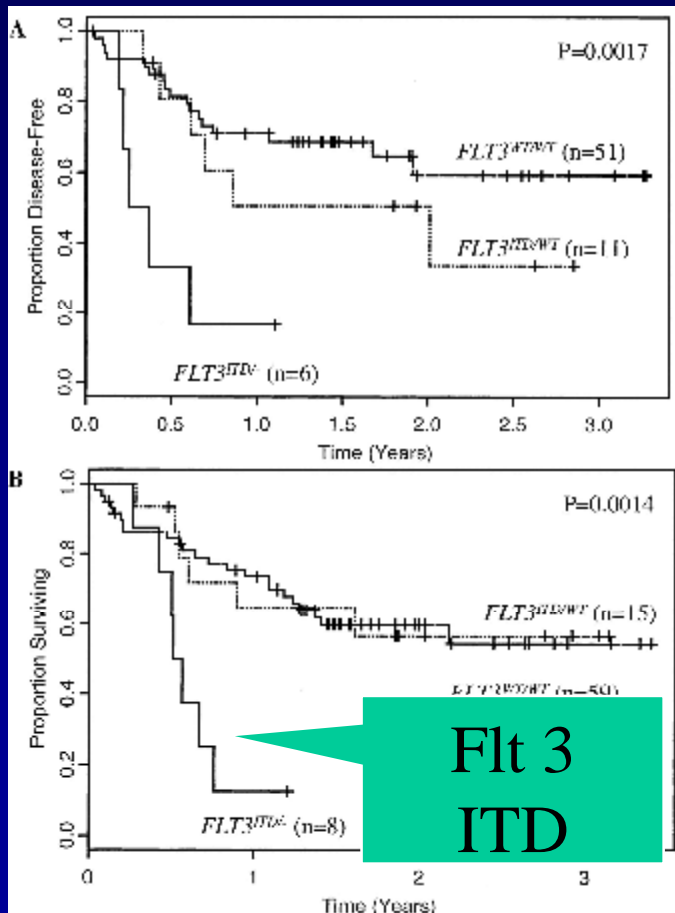
THEN

- We might design and conduct clinical trials only in Marker-positive patients

PKC 412/FLT3 Mutation Analysis

Co-Development

CALGB 10603



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Chemotherapy
+ Placebo

Chemotherapy
+ PKC 412

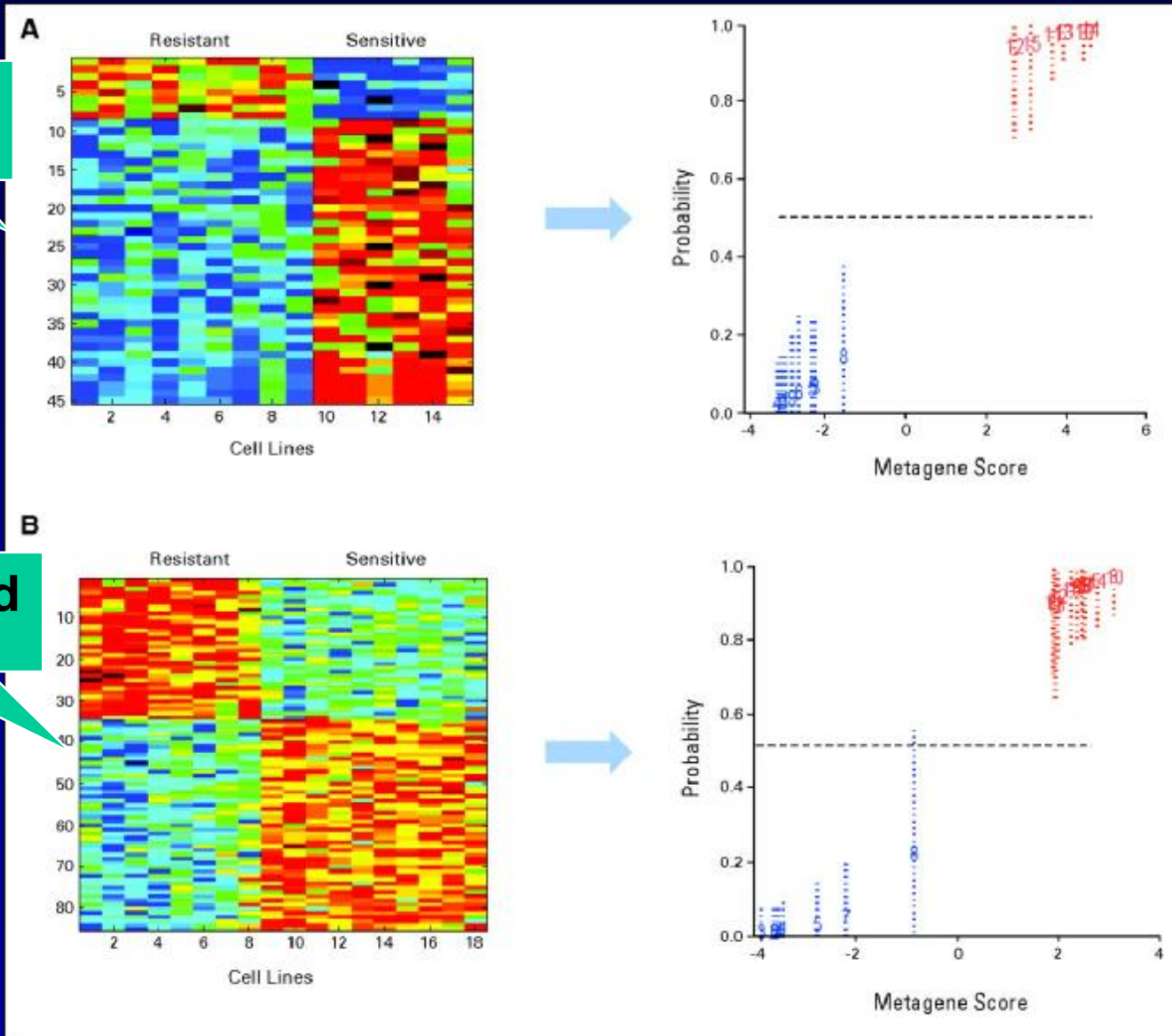
Maintenance
Placebo

Maintenance
PKC 412

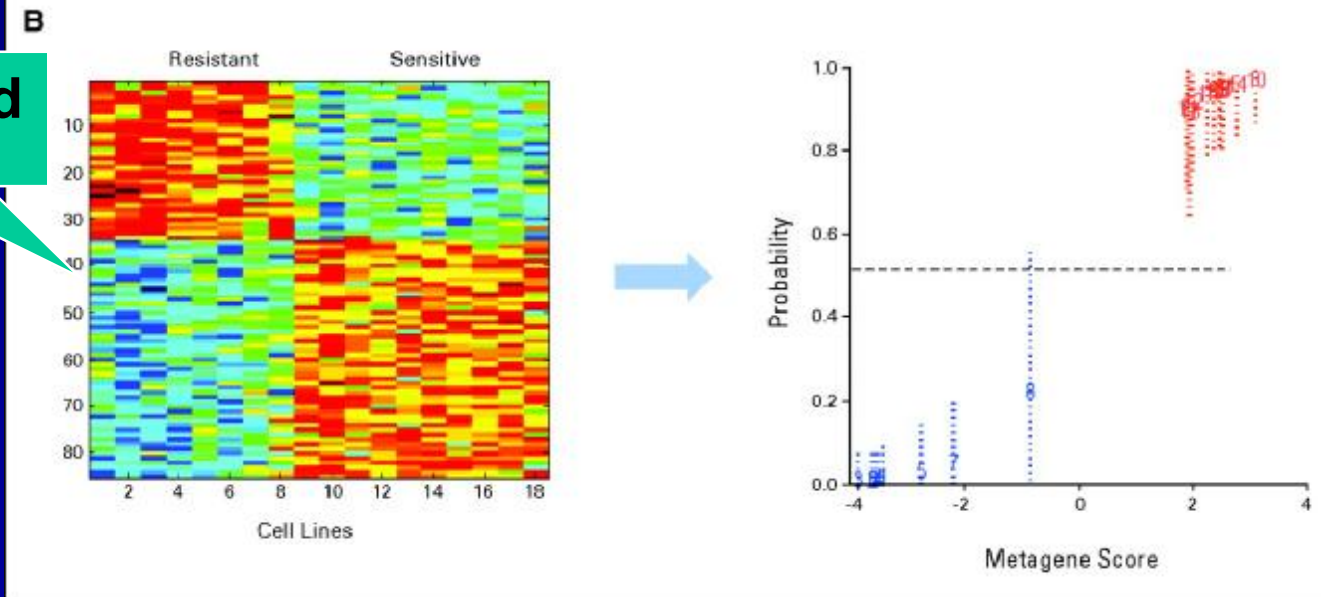
Prospective Biomarker Development Studies

Profiles of Drug Sensitivity

Cisplatin

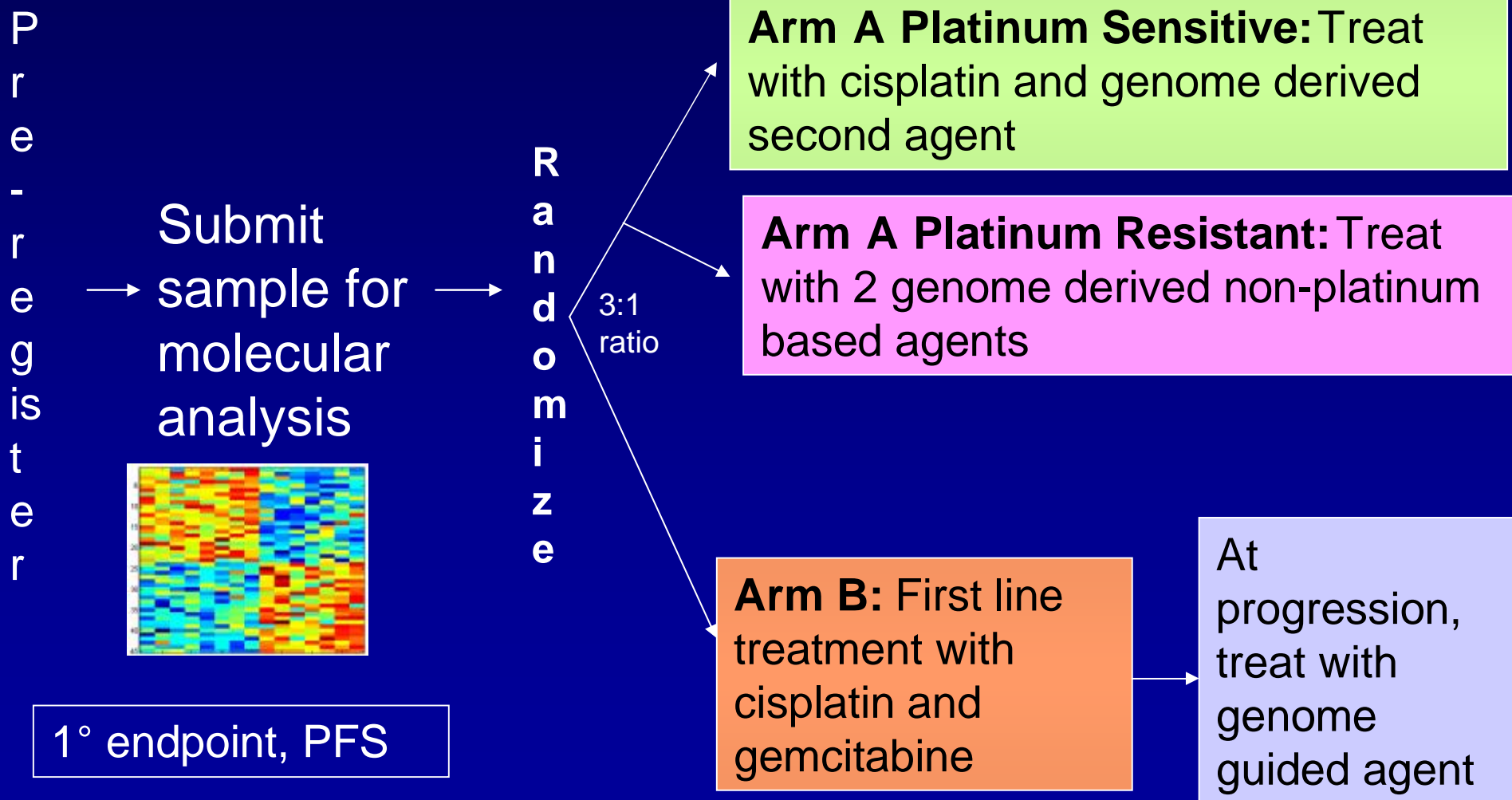


Pemetrexed

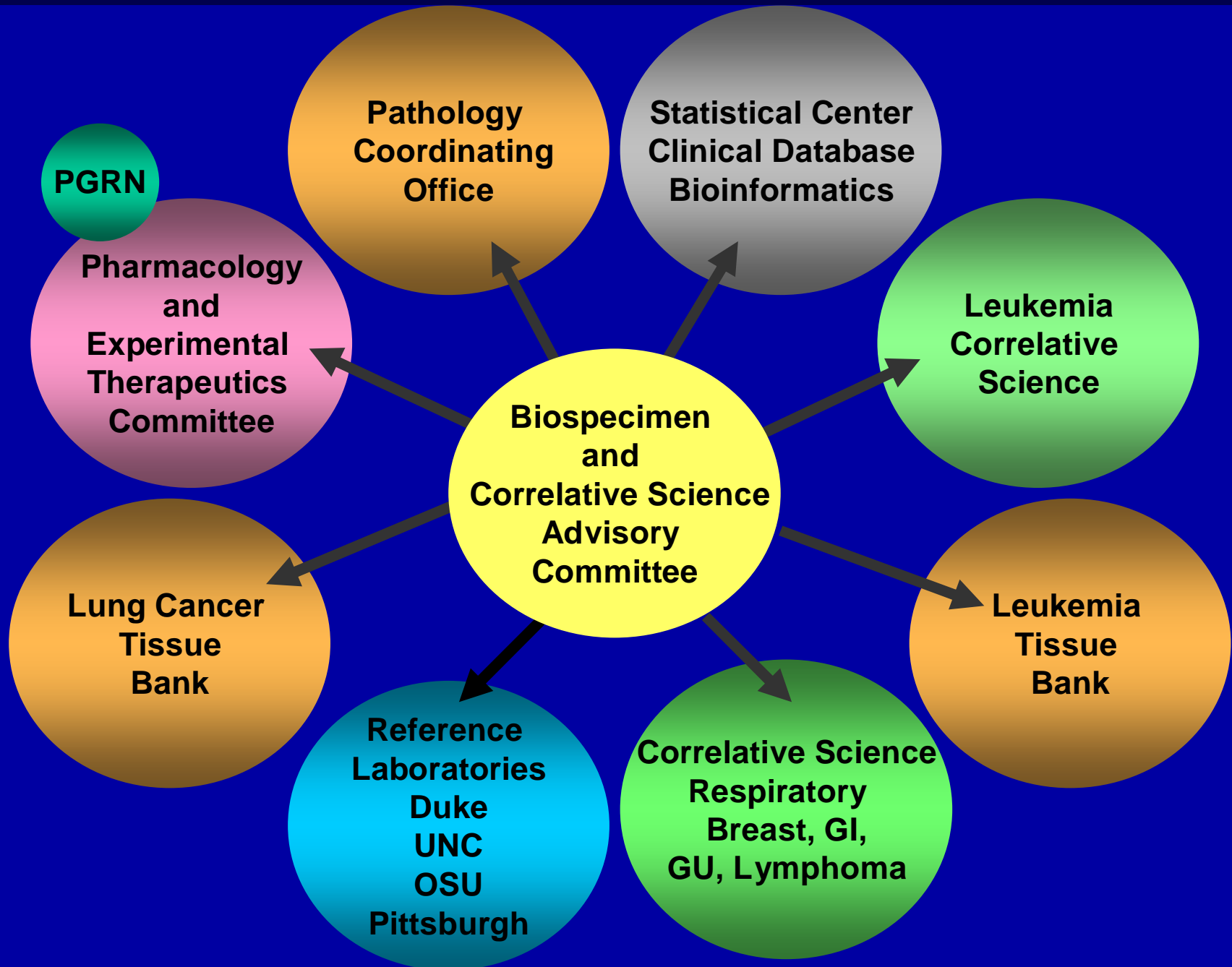


Hsu, D. S. et al. J Clin Oncol; 25:4350-4357 2007

CALGB 30702: Genome-guided chemotherapy for advanced stage NSCLC: A randomized phase II study



Translational Science Infrastructure



Obstacles to Biomarker Research in Cooperative Groups

- Adequacy of biospecimen collection at sites
- Access to CLIA-certified labs
- Funding for biomarker studies
- Regulatory requirements
- Contractual agreements with commercial partners, ownership of specimens, data, IP

Conclusions

- Cooperative groups have the capacity to conduct many types of biomarker studies, including formal validation trials
- Large numbers of patients are required for biomarker validation studies and even larger numbers may need to be screened
- Commercial partners essential to meet regulatory requirements and support the costs of biospecimen analysis